PHARMACEUTICAL PREPARATION WITH CYCLOSPORIN A

1. FIELD OF THE INVENTION

[0001] The invention relates to pharmaceutical preparations which contain an effective amount of cyclosporin A in combination with emulsifying vitamin E derivatives and a further emulsifier.

2. PRIOR ART

[0002] Cyclosporin A is a cyclic, water-insoluble, non-polar undecapeptide. The compound is a highly effective immunosuppressant, obtained from fungal cultures (Cane et al., Transplant TROC. 13, 349-358 (1981); Ferguson et al., Surgery 92, 175-182 (1982)). The medicament is employed to prevent the rejection of transplanted allogenic organs (Bennett & Norman, Arzn. Rev. Med. 37, 215-224 (1986); Van Basen, Surg. Clin. North Am. 66, 435-449 (1986)). Its immunosuppressive effect is based on a selective inhibition of cell function, which allows a survival of, for example, heart transplants without myelocyte suppression (Myers et al., New England Journal of Medicine 311, 699 (1984)). Additionally to use in transplantations, more recent clinical trials have shown that cyclosporin A is effective in the treatment of a large number of autoimmune disorders. For example, clinical trials were carried out on the treatment of polymyositis, systemic lupus erythematosus, rheumatoid arthritis or even of juvenile insulin-dependent diabetes (see the corresponding chapter in: Cyclosporine in Autoimmune Diseases, Editor Schindler, Springer Verlag, Berlin 19995 [sic]).

[0003] Cyclosporin A is a lipophilic molecule having a molecular weight of 1,202 daltons. On account of the poor water solubility and the high lipophilicity of cyclosporin A, its pharmaceutical compositions with customary solid or liquid pharmaceutical excipients often have disadvantages. Thus the cyclosporins are not adequately absorbed from such compositions (Cavanak & Sucker, Formulation of Dosage Forms, Prog. Allergy 38, 65-72 (1986)), or the compositions are not well tolerated, or they are not adequately stable on storage, for example against the crystallization of cyclosporin. Often the dissolved concentration in relation to the dose of up to 1 g daily is low, e.g. only 3%, which means the administration of 30 g of solution. A higher solubility is mentioned in DE-B-2 907 460, in which a solution of cyclosporin in vegetable oil, such as olive oil or maize oil, ethanol and an emulsifier consisting of a non-ionic ester of a triglyceride with a polyalkylene glycol is described. Examples of the preferred compositions given by this patent are drinking solution, drinking emulsion, injection solution and solution in capsules.

[0004] The administration of the above composition is preferably carried out intramuscularly or subcutaneously or, in particular, orally. Cyclosporin A, administered with the above pharmaceutical forms, is distinguished by a good bioavailability. After absorption, the substance binds rapidly to plasma proteins and has a terminal half-life of 24 hours. It is metabolised to a high percentage in the liver, biliary excretion being the main elimination route (Beverige, Cyclosporin A; in: Proceedings of International Symposium, Cambridge, editor White, pages 35-44 (1982)).

[0005] In spite of the: great value as an immunosuppressant, the clinical use of cyclosporin A is limited by the main side affect in chronic use, which is the nephrotoxicity of the active compound itself (Van Buren, Surg. Clin. North Am. 66, 435-449 (1986)). In about 80% of the kidney transplantation patients, renal toxicity also occurs (Kahan, Dial. Transplant. 12, 620-30 (1983)), mainly due to this substance-inherent side effect, which is used for the protection of the transplant from rejection.

[0006] Frequent side effects of cyclosporin treatments in various autoimmune disorders include, in addition to nephrotoxicity, hypertension, hyperkalaemia, hyperuricoaemia [sic], hepatotoxicity, anaemia, hypertrichiosis [sic], gingival hyperplasia, gastrointestinal side effects, tremor and paresthesia (Von Graffenried et al., Cyclosporine in Autoimmune Diseases, Editor Schindler, Springer Verlag, Berlin, pages 59-73 (1985)). Of the side effects mentioned here, the most frequent is nephrotoxicity. The acute nephrotoxicity induced by cyclosporin is dose-dependent and correlates with the cyclosporin blood levels. It is reversible after dose reduction or after completion of cyclosporin therapy (Chapman et al., Lancet I, 128 (1985)).

[0007] Acute cyclosporin nephrotoxicity is accompanied morphologically by tubular lesions which are characterized by inclusion bodies, isometric vacuolization and microcalcification (Mihatsch et al., Transplant. Proc. 15, 2821 (1983)). This leads to a decrease in the glomerular filtration rate, as can be detected on the basis of the rapid rise of serum creatinine in cyclosporin-treated patients. A reason for this could be the perturbation of the microcirculation by interaction of cyclosporin with the local prostacyclin synthesis (Neild at al.; in: Cyclosporine, editor Kahan, Gruen & Stratton, Orlando, Fla., page 182 (1984)).

[0008] Although the mechanism of renal dysfunction has still not been completely clarified, it was possible to show that, the renal synthesis of thromboxane occurs during the progress of immune- and non-immune-mediated models of renal damage (Lianos at al., J. Clin. Invest. 72, 1439-1448 (1983), Okegawa at al., J. Clin. Invest. 71, 81-90 (1983)). Thromboxane is a prostanoid and thus a metabolite of arachidonic acid from the cyclooxygenase cycle. The other prostanoids are prostaglandins and prostacyclins. Prostanoids are very effective mediators which are found during immunologically generated inflammation processes. They can basically change the renal haemodynamics (Morley; in: Lymphokines, editor Pic, Academic Press, New York, 4, 377-391 (1981)).

[0009] EP-A-0 305 400 describes the connections between disordered prostanoid synthesis and nephrotoxicity. According to this the administration of cyclosporin is accompanied by an increased synthesis of thromboxane B2, a mediator of inflammations. Cyclosporin should accordingly also promote the formation of prostaglandins of the E series, also inflammation mediators. It was possible to connect the rejection of human kidney transplants with a rapid rise in renally eliminated thromboxane B2.

[0010] EP-A-0 305 400 furthermore describes the use of w3-unsaturated fatty acids [sic] in combination with cyclosporin A for the inhibition of prostaglandin or thromboxane formation.

[0011] A disadvantage of the longer-term w3-fatty acid [sic] administration is the formation of a vitamin E deficiency state. Deficiency states are, for example, haemolysis